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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 49

Application Number	09/844,544
Filing Date	April 27, 2001
First Named Inventor	ZENG, DEFU
Group Art Unit	1644
Examiner Name	DIBRINO, MARIANNE
Attorney Docket Number	STAN-190

ENCLOSURES (check all that apply)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
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- ☐ Request for Refund
- ☐ CD, Number of CD(s
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group *(Appeal Notice, Brief-in triplicate, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below):*
  1. **Copy of Non-compliance notice**
  2. **Communication**
  3. **Declaration in triplicate**
  4. **Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	PAMELA J. SHERWOOD, 36,677 BOZICEVIC, FIELD & FRANCIS, LLP
Signature	Pamela Sherwood
Date	January 31, 2005

EXPRESS MAIL LABEL NO. EV519869415US

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COMMUNICATION

Address to:
Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket	STAN-190
Confirmation No.	3043
First Named Inventor	ZENG, DEFU
Application Number	09/844,544
Filing Date	April 27, 2001
Group Art Unit	1644
Examiner Name	DIBRINO, MARIANNE NMN
Title	"METHODS FOR INHIBITION OF POLYCLONAL B CELL ACTIVATION AND IMMUNOGLOBULIN CLASS SWITCHING TO PATHOGENIC AUTOANTIBODIES BY BLOCKING CD1-MEDIATED INTERATIONS"

Sir:

The attached Appeal Brief is submitted in triplicate, in response to the Notification of Non-Compliance dated January 10, 2005. Applicants note that the Notification of Non-Compliance states that such submission must be made in triplicate, although such is not required under current practice as set forth in 37 C.F.R. section 41.37.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number **STAN-190**

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 31, 2005

By: _____
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,544	04/27/2001	Defu Zeng	STAN 190	3043

24353 7590 01/10/2005

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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

01/14/05
Appeal Brief 02/10/05
LD 07/10/05

Notification of Non-Compliance With 37 CFR 1.192(c)	Application No. 09/844,544	Applicant(s) ZENG ET AL.	
	Examiner DiBrino Marianne	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *29 October 2004* is defective for failure to comply with one or more provisions of 37 CFR 1.192(c). See MPEP § 1206.

To avoid dismissal of the appeal, applicant must file IN TRIPLICATE a complete new brief in compliance with 37 CFR 1.192(c) within the longest of any of the following three **TIME PERIODS**: (1) **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer; (2) **TWO MONTHS** from the date of the notice of appeal; or (3) within the period for reply to the action from which this appeal was taken. **EXTENSIONS OF THESE TIME PERIODS MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 1.192(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, pending or cancelled, or does not identify the appealed claims (37 CFR 1.192(c)(3)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 1.192(c)(4)).

4. ☐ The brief does not contain a concise explanation of the claimed invention, referring to the specification by page and line number and to the drawing, if any, by reference characters (37 CFR 1.192(c)(5)).

5. ☐ The brief does not contain a concise statement of the issues presented for review (37 CFR 1.192(c)(6)).

6. ☐ A single ground of rejection has been applied to two or more claims in this application, and

   (a) ☐ the brief omits the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet presents arguments in support thereof in the argument section of the brief.

   (b) ☐ the brief includes the statement required by 37 CFR 1.192(c)(7) that one or more claims do not stand or fall together, yet does not present arguments in support thereof in the argument section of the brief.

7. ☐ The brief does not present an argument under a separate heading for each issue on appeal (37 CFR 1.192(c)(8)).

8. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 1.192(c)(9)).

9. ☒ Other (including any explanation in support of the above items):

The brief must contain the following items under the following headings in the order listed and with the proper content as per Rules of Practice before the BPAI effective September 13, 2004 (section 41.37):
i. Real party in interest
ii. Related appeals and interferences
iii. Status of claims
iv. Status of amendments
v. Summary of claimed subject matter
vi. Grounds of rejection to be reviewed on appeal
vii. Argument
viii. Claims appendix
ix. Evidence appendix
x. Related proceedings appendix

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

EXPRESS MAIL: EV519869415US January 31, 2005

Attorney Docket	STAN-190
First Named Inventor	D. Zeng
Application Number	09/844,544
Filing Date	April 27, 2001
Group Art Unit	1644
Examiner Name	M. Dibrino
Title: *Methods for Inhibition of Polyclonal B Cell and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions*	

Commissioner for Patents
Alexandria, VA 22313

BRIEF ON APPEAL

I. REAL PARTY IN INTEREST

The real party in interest is The Board of Trustees of the Leland Stanford Junior University, to which all rights have been assigned, as evidenced by the assignment recorded on April 27, 2001, reel and frame 011771/0601.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

The present application was filed on April 27, 2001 with original claims 1-14 pending. Following the Restriction Requirement of October 2, 2002, claims 3, 11 and 14 were withdrawn from consideration. In Applicants response of June 6, 2003, claims 4-5 and 9 were canceled. In Applicants response of December 19, 2003, claims 3, 11 and 14 were canceled. The presently pending claims are 1-2, 6-8, 10, 12 and 13.

IV. STATUS OF AMENDMENTS

During prosecution of the present application, on June 6, 2003, a response to the Office Action dated February 12, 2003 was filed amending claims 1, 6, 8, 10 and 13 and canceling claims

4-5 and 9, which amendment was entered. On December 19, 2003, a response to the Final Office Action dated October 21, 2003 was filed, canceling claims 3, 11 and 14, and amending claim 1. The Advisory Action of April 8, 2004 stated that the Amendments would be entered for purposes of appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Certain autoimmune diseases are the result of polyclonal stimulation of B cells and overproduction of antibodies, particularly autoantibodies of a pathogenic isotype. Systemic lupus erythematosus (SLE) is an example of an autoimmune disease characterized by polyclonal B cell activation, which results in a variety of anti-protein and non-protein autoantibodies. These autoantibodies form immune complexes that deposit in multiple organ systems, causing tissue damage. SLE is a difficult disease to study, having a variable disease course characterized by exacerbations and remissions. Disease manifestations result from recurrent vascular injury due to immune complex deposition, leukothrombosis, or thrombosis. Additionally, cytotoxic antibodies can mediate autoimmune hemolytic anemia and thrombocytopenia, while antibodies to specific cellular antigens can disrupt cellular function. (page 1, lines 1-11, paragraph 1)

Independent Claim 1 recites a method of treating pathogenic polyclonal B cell activation or class switching in a patient, the method comprising: administering to said patient an effective dose of a CD1 blocking antibody or fragment thereof, wherein said antibody or fragment thereof binds to CD1, and interferes with T cell recognition of CD1; wherein said dose is effective to reduce the pathogenic symptoms of said polyclonal B cell activation or class switching.

Pathogenic polyclonal B cell activation and class switching refers to autoimmune diseases wherein the primary pathology results from polyclonal stimulation of B cells resulting in overproduction of antibodies, particularly autoantibodies, and more particularly autoantibodies of a pathogenic isotype. The inappropriate activation or class switching of B cells may result from one or more of: dysfunctional expression of B cell activating cytokines; loss of B cell tolerance; T cell recognition of autoantigens and immunogens; mimicry of self-antigens by exogenous antigens; and the like. Of particular interest are diseases that are associated with CD1 mediated antigen presentation, *e.g.* systemic lupus erythematosus. (page 6, lines 1-10, paragraph 21)

CD1 is a nonpolymorphic, class I MHC-like, non-MHC encoded molecule that may be found non-covalently associated with β_2-microglobulin (β_2m). CD1 molecules have been demonstrated to be antigen-presenting molecules for glycolipid and hydrophobic peptides. A natural ligand of murine

CD1d has been reported to be glycosylphosphatidylinositol (GPI). (page 7, lines 19-25, paragraph 27).

CD1 blocking agents are molecules that interfere with the binding of CD1 by the T cell antigen receptor, for example by competitive or non-competitive binding to the extracellular domain of CD1, or to T cell antigen receptors that recognize CD1. Usually the binding affinity of the blocking agent will be at least about 100 μM. The blocking agent will be substantially unreactive with related molecules to CD1, e.g. Class I MHC antigens. Further, blocking agents do not activate CD1 signaling. Conveniently, this may be achieved by the use of monovalent or bivalent binding molecules. (page 8, lines 28-page 9, line 4, paragraph 32). Antibodies are a preferred blocking agent. (page 9, line 12, paragraph 34)

In the presently claimed methods, blocking antibodies, which specifically interact with CD1 antigen recognition, but do not activate signaling, are administered to a patient, and act to inhibit the function of T cells that recognize CD1. When CD1 mediated signaling is thus blocked, the T cell response is diminished, resulting in reduced polyclonal B cell activation and Ig class switching. Treatment with anti-CD1 monoclonal antibodies significantly delays the onset of proteinuria, reduces the levels of serum IgG and anti-dsDNA IgG and prolongs survival in a model system for SLE. (page 3, lines 10-20, paragraph 12)

T cells that recognize peptides derived from nucleosomes or anti-DNA antibodies augment the secretion of pathogenic anti-DNA IgG antibodies in a model for SLE. However, it has not been understood how conventional T cells recognizing peptides associated with MHC molecules can provide help for B cells secreting antibodies that are directed to non-protein antigens. (page 26, lines 9-18, paragraph 87)

The present invention demonstrates that an interaction between CD1 expressing B cells and CD1 reactive T cells play an important role in the development of lupus, and that the progression of disease can be inhibited by the administration of blocking reagents that interfere with CD1 mediated signaling. (page 28, lines 21-24, paragraph 92)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-2, 6-8, 10 and 12 have been rejected under 35 U.S.C. 103(a) as unpatentable over Amano *et al.* in view of Kotzin *et al.*, Zeng *et al.*, Blumberg *et al.* and Hughes.

Claim 13 has been rejected under 35 U.S.C. 103(a) as unpatentable over Amano *et al.* in view of Kotzin *et al.*, Zeng *et al.*, Blumberg *et al.* and Hughes, further in view of the Merck Manual.

VII. ARGUMENT

CLAIMS 1-2, 6-8, 10 AND 12 ARE PATENTABLE UNDER 35 U.S.C. 103(A) OVER AMANO *ET AL.* IN VIEW OF KOTZIN *ET AL.*, ZENG *ET AL.*, BLUMBERG *ET AL.* AND HUGHES.

Appellants respectfully submit that the presently claimed invention is not made obvious by the cited prior art. The present claims are directed to a method of treatment for pathogenic polyclonal B cell activation or class switching in a patient by the administration of antibodies or fragments thereof that bind to CD1 and interfere with T cell recognition of CD1.

Key to the invention is the demonstration provided by Appellants that *in vivo* blocking of CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-dsDNA autoantibodies, and delayed disease progression. Importantly, these results were obtained with a spontaneous disease model representative of clinical disease. The present invention is based on results that were unexpected in view of the cited art.

As will be shown below, the prior art teachings of the primary reference Amano *et al.* (and the work of Zeng *et al.*, which is cited by Amano *et al.*) relate to work with animals that were made to be transgenic for a T cell receptor that recognizes CD1. These transgenic animals do not develop any pathogenic polyclonal B cell activation. Specific subpopulations of transgenic T cells from these animals can be transferred to cause disease, but at the same time, other populations of these transgenic T cells, which are more representative of native populations, suppress disease.

From the teachings of the prior art, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in spontaneous lupus. Although the art suggested a possible connection between spontaneous lupus and CD1, there was substantial uncertainty that CD1 had a causative role, or was merely associated with the disease in these systems. Without the findings provided in the present application, one of skill in the art could not have a reasonable certainty of success practicing the claimed methods.

Indeed, in some instances prior art teaches away from the present invention. Prior to Applicants showing of the involvement of CD1 reactive cells (NKT cells), it was believed that the NKT cells were protective for lupus, not causative (see Takeda *et al.* (1993) J. Exp. Med. 177:155).

The Patent Office has cited Amano *et al.* as a primary reference. Amano *et al.* demonstrate that a T cell clone with an invariant Vβ9/Vα4.4 rearrangement proliferated in response to a B cell line

transfected with CD1 encoding sequences. The T cell clone also proliferated in response to splenic LPS-activated wild type cells, which response was inhibited by the monoclonal antibody 3C11.

What these experiments show is that certain T cell clones, which are isolated and grown in culture, and which have a specific invariant rearrangement of the T cell receptor, are able to recognize CD1 as a stimulating antigen (for example, see Amano *et al.* page 1714, under the heading "T cell recognition is not associated with β_2m").

In the specific teachings of the primary reference, Amano *et al.* identify two subpopulations of splenic B cells that express high levels of a ß2m-dependent form of CD1. Amano *et al.* go on to suggest that T cell recognition of CD1 on the surface of B cells might play a role in the pathogenesis of systemic lupus. The basis for this assertion is the finding that $CD4^+$ and $CD8^+$ T cells expressing anti-CD1 TCR transgenes obtained from a Vß9/V4.4 T cell clone will induce lupus when transferred into syngeneic BALB/c nude hosts. Amano *et al.* then cite the Zeng *et al.* (1998) paper to support this position[1].

It is important to the understanding of the unexpected results in the present patent application that one understand the cells involved in recognition of CD1. CD1 is not an antigen for conventional T cells, which are restricted to the major histocompatibility antigens by their receptor. However, there is another class of cells, termed NKT cells, termed NK T cells, which are neither typical T cells nor typical NK cells, but which bear an α/β antigen receptor, ands some of the markers typical of NK cells. These cells have a restricted antigen receptor repertoire, predominantly made up of an invariant rearrangement of the Vα14 and Jα281 gene segments, associated with Vβ7 or Vβ8 receptor. This receptor seems to be restricted to interacting with glycolipid antigens presented by the cell-surface molecule, CD1. NKT cells are also apparently limited in their cytokine repertoire.

A major drawback of the work published by Amano *et al.*, and Zeng *et al.*, is the use of a transgenic animal model, which requires transferring disease causing T cells into an immune compromised recipient. In this model, transgenic animals were created which had transgenic T cell receptors that recognized CD1. The transgene is then expressed in a majority of T cells in the animal. But because these coding sequences are artificially introduced, expression is not restricted to the NKT cell population, but rather is found on conventional T cells, which have different properties that NKT cells. The transgenic cells used in this work are (a) artificially found at a very

---

1 Reference 33 of Amano *et al.*

high concentration; (b) artificially expressing a receptor on a different class of cells and (c) artificially transferred into a host animal.

Because of the many artificial features of this model system, one could not draw any conclusions, certainly not conclusions with reasonable certainty, about the role of CD1 in lupus. In particular, the subset of cells that express the transgene is an important point.

Amano *et al.* report a double negative cell line that is **$CD4^-CD8^-$**, which expresses the Vβ9/Vα4.4 receptor, and which proliferates in response to CD1. The same T cell receptor, when expressed as a transgene, was associated with single positive cells (**$CD4^+CD8^-$** or **$CD4^-CD8^+$**) in one transgenic mouse; and with double negative cells (**$CD4^-CD8^-$**) in another mouse (see Zeng *et al.* page 526, last paragraph).

The key importance of this is that the injection of the double negative cells, which correspond to the cells that originally expressed the transgene, were **protective of disease**, while the single positive cells, which do not correspond to the original cell type, **caused a disease** phenotype.

Therefore, the data presented by Zeng *et al.* (1998) (and thus cited by Amano *et al.*) demonstrate that animals transgenic for a T cell receptor that recognizes CD1 do not develop disease; and that certain populations of the T cells can be transferred to **cause** disease, while other populations of T cells **suppress** disease. From these findings, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in lupus.

One of skill in the art would not have reason to believe that the cells tested by Amano *et al.*, which expressed Vβ9/Vα4.4 in a double negative cell, would prevent disease. The only pathological cells were those that artificially expressed the Vβ9/Vα4.4 transgene in a single positive cell, and even then, only after transfer to a secondary animal host, while the primary transgenic animal does not develop disease.

Appellants respectfully submit that the secondary references do not remedy the deficiencies of the primary references. Blumberg *et al.* teaches the expression of CD1 on B cells, monocytes and Langerhans cells, but fails to demonstrate the effectiveness of blocking CD1 to treat lupus-like disease.

Hughes provides background for the use of antibodies as therapeutics, but fails to teach the usefulness of antibodies specific for CD1 in the treatment of lupus-like disease.

Kotzin reviews the pathology of lupus, in particular the clonal expansion of anti-DNA antibody-producing B cells. However Kotzin fails to teach an association of CD1 with the disease, and does not show the effectiveness of blocking CD1 to treat lupus-like disease.

Appellants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. Prior to the *in vivo* demonstration of efficacy provided herein, there was substantial uncertainty as to the correlation between CD1 and lupus, particularly with respect to causality.

CLAIM 13 IS PATENTABLE UNDER 35 U.S.C. 103(A) OVER AMANO *ET AL.* IN VIEW OF KOTZIN *ET AL.*, ZENG *ET AL.*, BLUMBERG *ET AL.* AND HUGHES, FURTHER IN VIEW OF THE MERCK MANUAL.

Appellants respectfully submit that the invention of Claim 13 is not made obvious by the cited combination of references. As discussed above, the prior art does not provide a reasonable expectation that administration of CD1 would be effective in treating lupus-like disease. The inclusion of a second therapeutic regimen is not relied upon for patentability, but is merely put forth as a variation on Appellants methods.

Based on the teachings of the prior art, one of ordinary skill in the art would not have a reasonable expectation of success for the presently claimed invention. Withdrawal of the rejection is requested.

Appellants respectfully request that the rejection of 1-2, 6-8, 10, 12 and 13 under 35 U.S.C. 103 be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Bozicevic, Field and Francis LLP

Date: 01-31-05

Pamela J. Sherwood, Ph.D.
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VIII. CLAIMS APPENDIX

1. A method of treating pathogenic polyclonal B cell activation or class switching in a patient, the method comprising:

administering to said patient an effective dose of a CD1 blocking antibody or fragment thereof, wherein said antibody or fragment thereof binds to CD1, and interferes with T cell recognition of CD1;

wherein said dose is effective to reduce the pathogenic symptoms of said polyclonal B cell activation or class switching.

2. The method according to Claim 1, wherein said pathologic polyclonal B cell activation or class switching results in systemic lupus erythematosus.

6. The method according to Claim 1, wherein said antibody is a monoclonal antibody.

7. The method according to Claim 6, wherein said monoclonal antibody is a human or humanized antibody.

8. The method according to Claim 6, wherein said monoclonal antibody specifically binds to human CD1d.

10. The method according to Claim 6, wherein said antibody comprises a cocktail of monoclonal antibodies that bind to multiple human CD1 isotypes.

12. The method according to Claim 2, wherein said administration is by intravenous injection.

13. A method according to Claim 2, further comprising administering to said patient a second therapeutic agent which is an immunosuppressant, anti-inflammatory, or anti-coagulant agent for the treatment of systemic lupus erythematosus.

IX. EVIDENCE APPENDIX

A Declaration under 37 C.F.R. 1.132 was submitted with Appellants response of December 19, 2003; which was stated to have been considered in the Advisory Action of April 8, 2004. A copy is attached herewith.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Express Mail : EV333998300US	12/19/2003

Declaration under 37 C.F.R. 1.132

Mail Stop After Final
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P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket	STAN-190
First Named Inventor	D. Zeng
Application Number	09/844,544
Filing Date	April 27, 2001
Group Art Unit	1644
Examiner Name	M. Dibrino
Title: Methods for Inhibition of Polyclonal B Cell and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions	

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Samuel Strober, do hereby declare as follows:

I am a co-inventor of the above captioned patent application. I have read and understood the Office Action of October 21, 2003, and the references cited therein, particularly with respect to the rejection of claims 1, 2, 6, 7, 8, 10, 12 and 13 as being unpatentable over Amano *et al.* (1998), in view of Kotzin *et al.* (1996), Zeng *et al.* (1998); Blumberg *et al.* (1995) and Hughes (1998). I am also senior author of the cited Amano *et al.*, and Zeng *et al.* papers.

The present claims are directed to a method of treatment for pathogenic polyclonal B cell activation or class switching in a patient, by the administration of antibodies or fragments thereof that bind to CD1 and interfere with T cell recognition of CD1. Key to the invention is our demonstration *in vivo* that blocking CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-dsDNA autoantibodies, and delayed disease progression. Importantly, these results were obtained with a spontaneous disease model, in contrast to the prior art model, which required a highly artificial transfer of genetically modified cells. These results were unexpected in view of the cited art.

The Examiner has cited our work, published as Amano *et al.* (1998). It is stated in the Office Action that: "Amano et al. teach that the interaction between anti-CD1 T cells and B cells

expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *In vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano et al further teach that transgenic CD1 + T cells (Vb9/Va4.4 T cell clones) induce lupus (SLE, and autoimmune disease) when transferred into nude mice which do not spontaneously develop lupus and that spontaneous secretion of IgM and IgG by splenic B cells from lupus prone mice is mediated by CD1 hi subset of B cells."

The Office Action concludes that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by the use of the anti-CD1d mAb 3C11.

I note that as a matter of correctness, the experiments described above were published in the Zeng *et al.* paper, not by Amano *et al.*, although Amano *et al.* briefly refer to the work, without disclosing the underlying data.

It is critical to the understanding of the unexpected results in the present patent application, that one understand the cells involved in recognition of CD1. CD1 is not an antigen for conventional T cells, which are restricted to the major histocompatibility antigens by their receptor. However, there is another class of cells, termed NKT cells, ~~termed NK T cells~~, which are neither typical T cells nor typical NK cells, but which bear an α/β antigen receptor, ands some of the markers typical of NK cells. These cells have a restricted antigen receptor repertoire, predominantly made up of an invariant rearrangement of the Vα14 and Jα281 gene segments, associated with Vβ7 or Vβ8 receptor. This receptor seems to be restricted to interacting with glycolipid antigens presented by the cell-surface molecule, CD1. NKT cells are also apparently limited in their cytokine repertoire.

The work described by Amano *et al.* related to recognition of the CD1 molecule in the absence of β_2-microglobulin, a protein component required for MHC class I molecules to properly function in antigen presentation.

Amano *et al.* demonstrate that a T cell clone with an invariant Vβ9/Vα4.4 rearrangement proliferated in response to a B cell line transfected with CD1 encoding sequences. The T cell clone also proliferated in response to splenic LPS-activated wild type cells, which response was inhibited by the monoclonal antibody 3C11.

What these experiments show is that certain NKT cell clones, which are isolated and grown in culture, and which have a specific invariant rearrangement of the T cell receptor, are able to recognize CD1 as a stimulating antigen (for example, see 1714, under the heading T cell

recognition is not associated with β_2m). However, **these experiments do not show that B cells are stimulated by the T cell.**

It is a hallmark of lupus that the disease is associated with polyclonal B cell activation and class switching. The proliferation of T cells is interesting, but is not informative of a disease that is caused by B cells.

The work in my laboratory that is referred to in the above paragraph from the Office Action was published by Zeng *et al.* In this work, the T cell receptor noted by Amano *et al.* (Vβ9/Vα4.4), which was associated with proliferation in response to CD1, was cloned, and inserted as a transgene into an animal.

The transgene is then expressed in a majority of T cells in the animal. But because these coding sequences are artificially introduced, expression is not restricted to the NKT cells population, but rather is found on conventional T cells, which have different properties that NKT cells. The transgenic cells used in this work are (a) artificially found at a very high concentration; (b) artificially expressing a receptor on a different class of cells and (c) artificially transferred into a host animal.

Because of the many artificial features of this model system, one could not draw any conclusions, certainly not conclusions with reasonable certainty, about the role of CD1 in lupus. In particular, the subset of cells that express the transgene is an important point.

Amano *et al.* report a double negative cell line that is **$CD4^-CD8^-$**, which expresses the Vβ9/Vα4.4 receptor, and which proliferates in response to CD1. (see Amano *et al.*, page 1714, paragraph under the heading "T cell recognition of CD1 is not associated with β_2m"). On the other hand, the same T cell receptor, when expressed as a transgene, was associated with single positive cells (**$CD4^+CD8^-$** or **$CD4^-CD8^+$**) in one transgenic mouse; and with double negative cells (**$CD4^-CD8^-$**) in another mouse. (see Zeng *et al.* page 526, last paragraph).

The key importance of this is that the injection of the double negative cells, which correspond to the cells that originally expressed the transgene, were **protective of disease**, while the single positive cells, which do not correspond to the original cell type, **caused a disease** phenotype.

One of skill in the art would have reason to believe that the cells tested by Amano et al., which expressed Vβ9/Vα4.4 in a double negative cell, would prevent disease. The only pathological cells were those that artificially expressed the Vβ9/Vα4.4 transgene in a single positive cell, and even then, only after transfer to a secondary animal host, while the primary transgenic animal does not develop disease.

Therefore, the data presented by Zeng *et al.* (1998) demonstrate that animals transgenic for a T cell receptor that recognizes CD1 do not develop disease; and that certain populations of the T cells can be transferred to cause disease, while other populations of T cells, which are more representative of native populations, suppress disease. From these findings, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in spontaneous lupus. Although the art suggested a possible connection between spontaneous lupus and CD1, there was substantial uncertainty that CD1 had a causative role, or was merely associated with the disease in these systems. Without the findings provided in the present application, one of skill in the art could not have a reasonable certainty of success practicing the claimed methods.

I hereby declare that all statements made herein of my own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 12/18/03

By _____

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X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.